

Aceh International Journal of Science and Technology

ISSN: 2088-9860

Journal homepage: <http://jurnal.unsyiah.ac.id/aijst>



DFT and PM3 Computational Studies of the Reaction Mechanism of the Oxidation of L-Tyrosine by Iodine in the Gas Phase

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Received : May 14, 2014

Accepted : July 27, 2014

Abstract - The oxidation of L-Tyrosine by molecular iodine was studied using semi-empirical and density functional theory methods. Molecular information such as net charges, values of frontier orbital energies, composition, proportions and bonding contribution were obtained and analyzed. Thus, possible reactive sites were proposed and the reaction mechanism was postulated. The postulated transition states, intermediates and products were also computed using the PM3 and DFT methods. Computed enthalpies of the oxidation reaction at standard conditions for the PM3 and DFT calculation were 216.97 kJ/mol and -36327404.72 kJ/mol respectively. The calculated ΔG° and ΔS° , for the transition states according to the DFT model were both large and negative indicating that the processes were exergonic associative substitution reactions.

Keywords: L-Tyrosine; Iodine; Enthalpies; Transition states; Reaction mechanism

Introduction

The study of the oxidation of proteins and amino acids is of interest because of their biological significance and selectivity towards oxidant to yield different products (Laloo and Mahanti, 1990; Giulivi and Davies, 2001). Amino acids act not only as the building block in protein synthesis but also play a significant role in metabolism, nutrition, fortification of seeds, biochemical research and have been oxidized by a variety of oxidizing agents (Malika et al., 2010; Hung and Stanbury, 2005; Faller et al., 2002). L-Tyrosine (L-Tyr) is a nonessential or a semi-essential amino acid the body makes from another amino acid called phenylalanine (Hoffman et al., 2010; Xiashi and Suqin, 2010; Poustie and Wildgoose, 2010).

It is a building block for several important brain chemicals called neurotransmitters, including epinephrine, norepinephrine and dopamine (Webster and Wildgoose, 2013; Mahoney et al., 2007). L-Tyrosine is used for the treatment of tuberculosis, myelitis, encephalitis, thyroid bacterial infections and as a nutritional supplement. Parkinson's disease, albinism, depression, and other mood disorders were generally found when L-Tyrosine levels are abnormal (Gelenberg et al., 1982; Meyers, 2000; Parry, 2001). L-Tyrosine also helps produce melanin, the pigment responsible for hair and skin color. It helps in the function of organs responsible for making and regulating hormones, including the adrenal, thyroid, and pituitary glands. It is involved in the structure of almost every protein in the body (Azori et al., 1990; Bergès et al., 2011; Tumilty et al., 2011; Van Spronsen et al., 2001; Marquez and Dunford, 1995).

It has been reported (Klebanoff, 1967; Aghaie et al., 2008) that free Iodine reacts with the protein of bacteria (presumably by iodinating L-Tyrosine residues) and thus kills the bacterium organism. At pH= 6.8, Iodine reacts with tyrosine as well as with cysteine. Iodine deficiency is currently the most preventable cause of the world's cretinism, brain damage and thyroid disorders

as well as those of ovaries, breasts and prostate (Aghaie *et al.*, 2008; Cao-Xue *et al.*, 1994). These are just a few of the reasons why the study of Iodine as well as L-Tyrosine is interesting. Biologically, iodine is most essential in the synthesis of thyroid hormones, which serve in the differentiation, growth, metabolism and physiological function of virtually all tissues (Yen, 2001). In the thyroids colloid, iodide is collected and concentrated. After concentration, iodide is oxidized to I^+ by the enzyme thyroid peroxidase (TPO) in the presence of H_2O_2 . The oxidized Iodine is then bound to L-Tyrosine residues of the protein thyroglobulin to produce monoiodothyrosine (MIT) and diiodothyrosine (DIT). Thyroglobulin (Tg) acts as the substrate for thyroid hormone (T_3 , T_4) biosynthesis (Mallet *et al.*, 1995).

Despite the importance of both Iodine and L-Tyrosine, there seemed to be not many studies on their reaction mechanisms. Even when there is (Aghaie *et al.*, 2008), it appeared to be ambiguous or not conclusive. The present paper desired to report the results of computational studies on the mechanism of the oxidation of L-Tyrosine by iodine. The computational analyses of the structures using semi-empirical (PM3) and DFT (B3LYP) are reported. Computational chemistry methods can be used to explore the theoretical chemistry behind reactive systems, to compare the relative chemical reactivity of different systems, and, by extension, to predict the reactivity of new systems. Transition states for reaction of L-Tyrosine with iodine were determined; equilibrium states of reactants, intermediates and products were searched by computational means. The semi empirical models MNDO, AM1, and PM3 are often used in computational chemistry because they allow study of systems that are out of reach of more accurate methods. For example, modern semi-empirical programs allow study of molecules consisting of thousands of atoms while *ab initio* calculations that produce similar thermochemical accuracy are feasible on molecules consisting of less than 50-70 atoms (Young, 2002; Kahn and Bruice, 2000; Kahn and Tipton, 2000; Kahn, 1999; Stewart, 2007). Only the most suitable calculation results of the semi empirical method (PM3) were reported in this study (Castells *et al.*, 1980; Jordan, 1976; Shin *et al.*, 1993; Shaffer and Wierschke, 1993; Burling and Goldstein, 1992; Kabir and Sapse, 1991; Mari *et al.*, 1992).

In theoretical studies using *ab initio* or density functional theory (DFT) methods, adequate choices of a theoretical method and a basis set are very important in obtaining reliable results. Unfortunately, for elements beyond the 4th row in the periodic table, basis sets, are relatively limited, although various accurate theoretical methods such B3LYP have been currently developed. Theoretical studies on compounds containing iodine, a 5th period halogen atom, are less abundant compared to those containing F, Cl or Br which are 2nd, 3rd and 4th elements respectively. Heavy elements like Iodine have a large number of core electrons which are in general less important for the chemical reactivity and bonding modes. However, it needs a large number of basis sets or functions to describe the corresponding orbitals. This makes computations with heavy elements like Iodine very time consuming and expensive (Ayub and Mahmood, 2013; Zhang and Hase, 2010; Jensen, 1999). However, compounds containing Iodine atom play very interesting and important roles in many chemical reactions, especially in the life sciences. Despite the challenges therefore, this makes the study of Iodine quite interesting, especially with using the more exact method of DFT.

Materials and Methods

Materials

The Spartan '14 v1.1.0 semi-empirical (PM3) and DFT methods were used on Microsoft window XP professional version 2002 SP3 computer system, with Intel(R) Pentium(R) Dual CPU,E2200@2.20 GHz 219 GHz, 3.24GB of RAM.

Geometry optimization of reactants, intermediates, transition states and products

All the electronic structure calculations reported in this work were performed using the Spartan '14 v1.1.0 program packages. The geometries included in the reaction of L-Tyrosine with iodine were fully optimized using the semi-empirical method (Bingham *et al.*, 1975; Dewar

and Thiel, 1977; Dewar *et al.*, 1985; Stewart, 1989a; Stewart, 1989b). To check the influence of basis set, the AMI, PM3 of semi empirical methods and 6-311+G** basis set of DFT at the B3LYP levels of computation were employed to optimize the geometries of the reactants, intermediates, transition states and products. There was a little change in comparing geometrical parameters obtained by the semi empirical models (Schlegel, 1986; Kalkanis and Shields, 1991), but there were marked differences between the semi empirical methods and the DFT method. It thus indicated that the geometrical parameters were sensitive to the sizes of the basis sets or computational levels. The starting geometries for all of the semi-empirical calculations were at first optimized in the Spartan '14 v1.1.0 Global calculations environment work space at the AM1 level, and then followed by the PM3 calculations. The optimized geometries of the reactants, intermediates, transition states and products were confirmed in terms of vibrational analysis (Spartan, 1993).

The transition state for each step was located and confirmed by animating the vibration corresponding to the reaction coordinate by selecting the imaginary frequency at the top of the list of frequencies on the IR tab. No arbitrary assumptions was imposed on finding the most likely geometries for the transition state in each case.

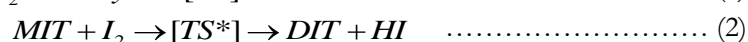
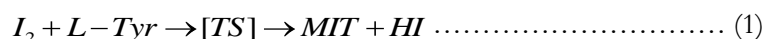
Calculation of molecular information

Molecular information including net charges, electron density, molecular orbital energies were calculated by selecting orbitals and energy, thermodynamics, vibrational modes, charges and bond orders in the calculation menu of the Spartan package before the submission of each species. The information gathered from these was then used in discussing the properties of the optimized species.

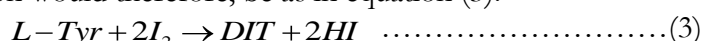
Results and Discussion

Published mechanism

The outline of the published mechanism of the oxidation of L- Tyrosine with Iodine as given by Aghaie *et al.* (2008) is shown in Figure 1. This figure can be presented in a simplified form as in equations 1 and 2.



The stoichiometric equation of the reaction would therefore, be as in equation (3).



Aghaie *et al.* (2008) were of the opinion that the transition state, [TS], in equation 1 can exist as different equilibrium conformers represented as [TS₁-TS₄] in Figure 1. It is the desire of this work to find out if all the conformers can exist, and if they do which one would be the most favorable one energetically; and thus propose a mechanism based on this finding.

Geometry optimization of intermediates and transition states including validity of the generally accepted mechanism

Geometry optimization of the reactants, intermediates, transition states and products in the L- Tyrosine reaction with Iodine was executed. The geometry optimizations of all these species were successfully completed and the heat of formation at 298.15K (ΔH°) were evaluated and presented together with other activation parameters in Table 1.

If we consider the heat of formation of the various optimized transition states as proposed by Aghaie *et al.*, (2008), TS₁ has the least enthalpy (932.15 kJ/mol) of formation, followed by TS₂ (1001.15 kJ/mol), TS₄ (1095.16 kJ/mol) and TS₃ (1204.04 kJ/mol) according to the PM3 calculations (Table 1). The trend with the DFT calculations was not quite different only that TS₂ was most favored and was therefore, the most stabilized of the four possible transition states (TS₁-TS₄). The energy diagrams (Figure 2 & Figure 3) showed the energy profiles of the optimized reacting species, where R₁ were the reactants in step 1, with TS₁₋₄ as the possible

transition states and P₁, the products of the same step; whereas R₂, TS* and P₂ were the reactants, transition state and products of the second step respectively.

Table 1. Heat of formation and other activation parameters of reacting species

S/ N	Reacting Species	Activation parameters at 298.15K using PM3 method			Activation parameters at 298.15K using DFT method		
		ΔH° (kJ/mol)	ΔG° (kJ/mol)	ΔS° (kJ/mol.K)	ΔH° (kJ/mol)	ΔG° (kJ/mol)	ΔS° (kJ/mol.K)
1	I ₂	114.05	36.73	259.34	-36334477.09		
2	L-Tyr	100.73	-37.67	464.22	-1654299.96		
3	TS ₁	932.88	798.38	451.10	-19817227.73	-36998.46	-66343.21
4	TS ₂	1001.15	844.71	524.69	-19817240.74	-36998.45	-66343.26
5	TS ₃	1204.04	1026.02	597.10	-19817216.84	-36998.46	-66343.18
6	TS ₄	1095.16	946.62	498.22	-19816905.20	-36998.49	-66343.17
7	MIT	513.01	-11.11	513.01	-19816427.88		
8	HI	119.36	57.88	206.18	-18168798.89		
9	TS*	258.21	43.51	720.09	-56143919.32	-40708.64	-17688.05
10	DIT	193.03	26.60	558.22	-37978585.13		

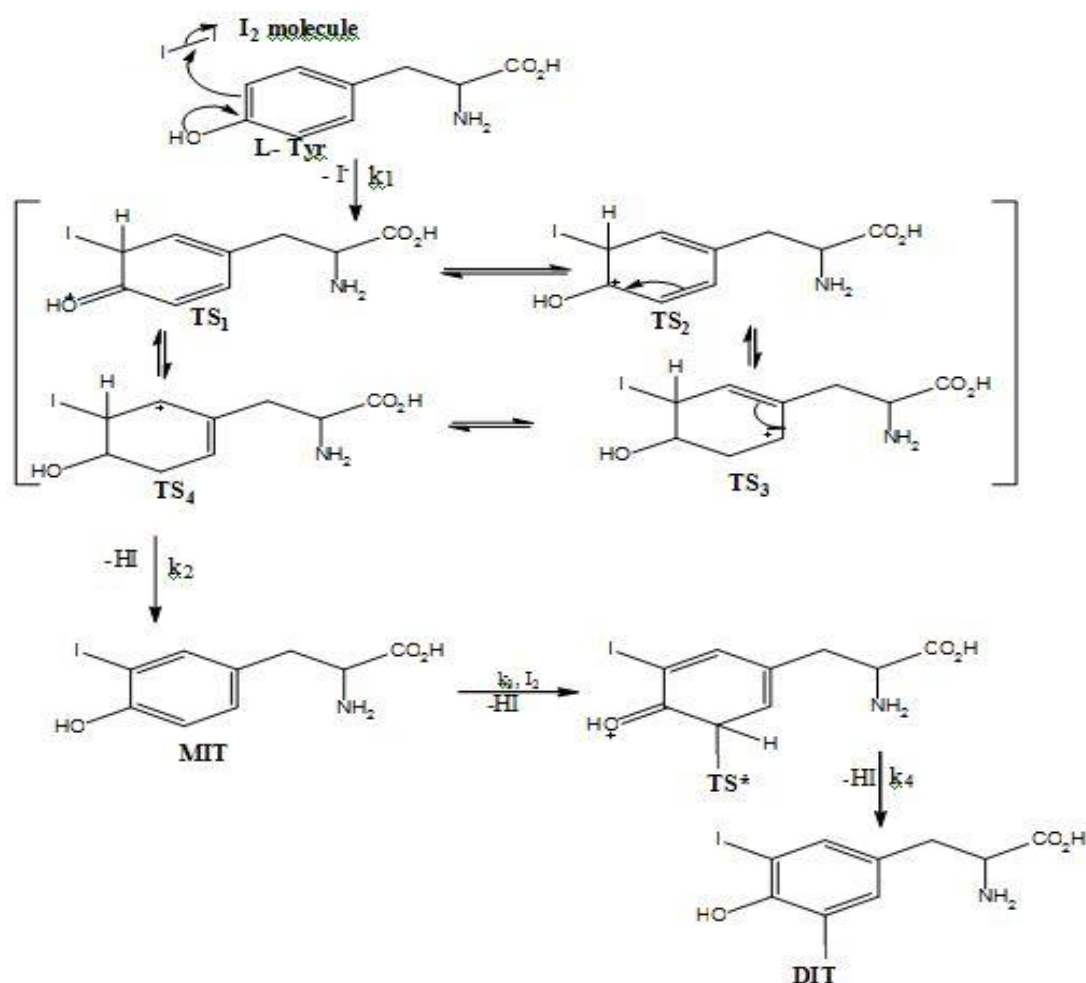


Figure 1. The reaction mechanism as proposed by Aghaie *et al.* (2008)

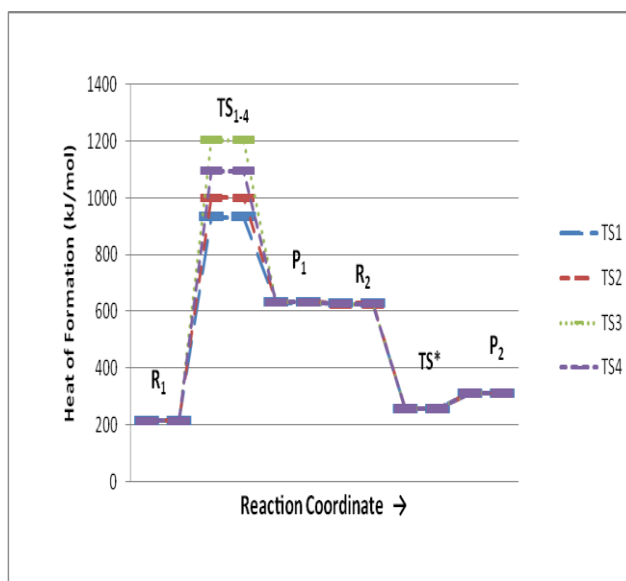


Figure 2. Energy profile of the oxidation of L- Tyrosine by iodine according to the PM3 calculations

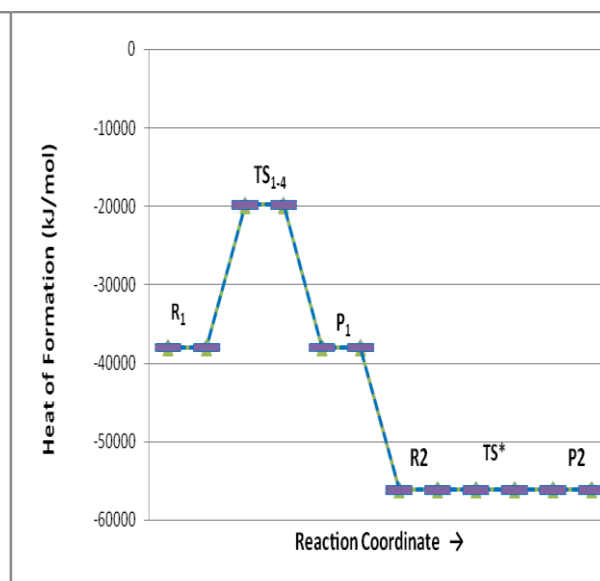


Figure 3. Energy profile of the oxidation of L- Tyrosine by iodine according to the DFT calculations

Figure 2 showed $TS_{1,4}$ as saddle points as expected but unfortunately failed to do for TS^* . This showed the deficiency of the semi-empirical calculations. Figure 3 was able to show $TS_{1,4}$ and TS^* as saddle points as expected because the accuracy of The DFT calculations. For the DFT calculations, the heat of formation energies for the various species ($R_2 = -56,150,904.97$ kJ/mol, $TS^* = -56,143,919.32$ kJ/mol and $P_2 = -56,147,384.02$ kJ/mol) were close but that of TS^* was still slightly higher.

Charge distribution

The starting L- Tyrosine molecule was optimized. The conformation with the lowest energy was optimized and calculated using the PM3 method. Then molecular information such as net charges, electron density, molecular orbital energies were obtained. The identity numbers of all non-hydrogen atoms of the conformer compound were labeled as in Figure 4.

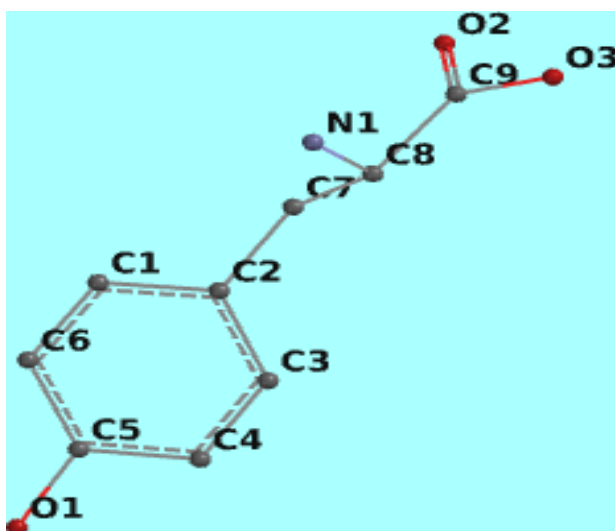


Figure 4. Labeled structure of L-Tyrosine

group can be stabilized or be made inactive when they form zwitter, they have not been

The more negative charges that an atom possesses, the more the ability of the atom to react with electrophiles. On the other hand, the more positive charges that an atom possesses, the more the capacity of the atom to react with nucleophiles or nucleophilic reagents. In this paper, the net charges as well as the exposed areas of non-hydrogen atoms of the reactant, L- Tyrosine, were shown in Table 2. Atoms C_1 , C_3 , C_4 , C_6 , C_7 , O_1 , N_1 , O_2 and O_3 , possessed more negative charges, while C_2 , C_5 , C_8 and C_9 possessed more positive charges. Among these, atoms C_4 , C_6 , N_1 , O_1 , O_2 and O_3 possessed the most net charges and were capable reactive sites with electrophiles. Because atoms N_1 of the amino group, O_1 of the hydroxyl group, and O_2 , O_3 of the carboxyl

considered (Laloo and Mahanti, 1990; Giulivi and Davies, 2001; Malika *et al.*, 2010; Faller *et al.*, 2002; Foppoli *et al.*, 1997; Trouillas *et al.*, 2011). Amino acids with aromatic side chain were oxidized more rapidly than the alkyl side chain amino acids. Thus, atoms C₄ and C₆ were the most reactive sites. The calculated exposed areas of the atoms also showed atoms C₄ and C₆ presented more surfaces for reactivity (Spartan, 1993).

Table 2. Net atomic charges and exposed surface of L- Tyrosine molecule

No.	Charge	Exposed surface (Å)	No.	Charge	Exposed surface (Å)
C ₁	-0.003753	13.11	C ₈	0.230113	5.13
C ₂	0.032617	4.88	C ₉	0.765132	13.12
C ₃	-0.015731	12.96	O ₁	-0.563147	11.44
C ₄	-0.304182	13.92	N ₁	-0.845714	7.88
C ₅	0.535871	9.10	O ₂	-0.531727	14.30
C ₆	-0.333762	13.68	O ₃	-0.553559	11.40
C ₇	-0.166882	8.69			

Molecular orbitals and frontier electron density

The plots of the HOMO and LUMO of L-Tyrosine were shown in Figure 5. It could be seen that the frontier electron densities of atoms C₄ and C₆ in both HOMO and LUMO orbitals were larger than those of the other atoms. These, according to Fukui's frontier orbital theory (Fukui, 1964; Fukui, 1974; Fukui, 1982; Ya-Yin *et al.*, 2002), coupled with the fact that these same atoms carried the most negative charges were pointers to their being the most capable reactive site in the molecule. In addition, the bonding contribution of LUMO (-21.95 kJ/mol) for bond cleavage was smaller than that of HOMO (-888.41 kJ/mol) for bond formation; thus it showed that there was bond formation between L-Tyrosine and the electrophiles. This may also indicate that the substitution reaction occurred by the associative interchange (I_a) mechanism, as there were both bond breakage and bond formation, with the bond formation dominating (Housecroft and Sharpe, 2008).

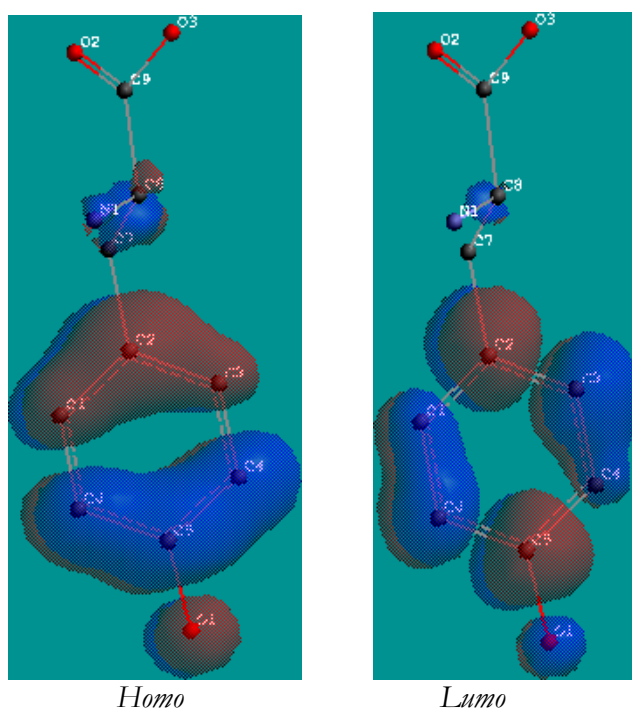


Figure 5. Plots of the HOMO and LUMO of L-Tyrosine molecule

Calculations of transition states and intrinsic reaction coordinates

Only the transition state production and the values of the active energies can really reveal whether the reactions occur or not and also how they occur if they do. In order to better understand the mechanism, dynamic calculations of the transition state was also investigated. The bond lengths of C₆-I, C₆-H and C₄-H (the reactive sites) of the various optimized transition states postulated by Aghaie *et al.* (2008) were examined to see if there were any differences. The results were as presented in Table 3.

Table 3. Bond lengths of the reactive sites the transition states

Transition states	Bond lengths (Å)		
	C ₆ -I	C ₆ -H	C ₄ -H
TS ₁	2.376	1.092	1.105
TS ₂	2.020	1.126	1.105
TS ₃	8.139	1.092	1.092
TS ₄	2.376	1.092	1.105

The bond lengths for C₆-H and C₄-H in the optimized L-Tyrosine (Figure 4) were 1.091 and 1.090 respectively while all the other C-H bond lengths were 1.092. In the activated complex, TS₂, the bond lengths for C₆-H and C₄-H increased from 1.091 and 1.090 to 1.126 and 1.105 respectively, thus indicating that the respective H-atoms were pushed further away from the respective C-atoms, ready to be replaced by incoming substituent. On the other hand, the same C-H bond lengths under consideration in TS₂, TS₃ and TS₄ remained unaffected. Also, considering the C₆-I bond lengths (Table 3) in TS₁, T₂, TS₃, and TS₄ respectively, TS₂ had the shortest bond length, and that also showed that the C-I bond in TS₂ was more stabilized than in the others.

Proposal of a more plausible mechanism for the reaction

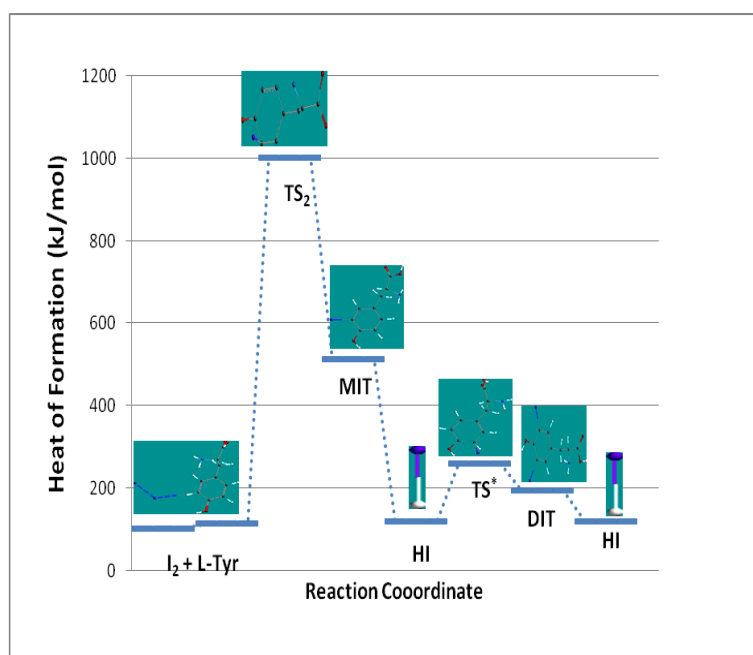


Figure 6. Energy profile of the oxidation of L- Tyrosine by iodine showing the position of the optimized reacting species

Based on the discussion of the optimized L-Tyrosine's activated C₄ and C₆, the net charges, electron density, molecular orbital energies, the heat of formation of the various proposed transition states and their C₄-H, C₆-H, C₆-I bond lengths, it became obvious that TS₂ was the most stabilized and favored transition state, and therefore, the reaction mechanism would be as given in the Figure 6.

Enthalpy of reaction and rate constant calculations (Ochterski, 2000; Engel and Reid, 2006). The enthalpies of reaction were calculated by using the Spartan software package to calculate heats of formation at standard temperature of 298.15K and the appropriate sums and differences

taken as given in equation (4).

$$\Delta_r H^\circ_{298.15K} = \sum_{\text{products}} \Delta_f H^\circ_{298.15K} - \sum_{\text{reactants}} \Delta_f H^\circ_{298.15K} \dots\dots\dots (4)$$

The mechanism proposed here is still consistent with that published by Aghaie *et al.*, (2008) only that the transition state, TS₂, for step1 which was also the rate determining step (Figure 1), was found to be more favorable for all the reasons highlighted above. TS₂ was therefore adopted as shown in Figure 3, while TS₁, TS₃ and TS₄ were rejected for the same reasons discussed above. Computed enthalpies of the oxidation reaction at standard conditions for the PM3 and DFT calculation were 216.97kJ/mol and -36327404.72kJ/mol respectively. Other activation parameters of the reaction at standard conditions, ΔG° and ΔS° , for the PM3 studies were calculated by the Spartan software package by default and were as provided in Table 1. ΔG° and ΔS° for the DFT studies were computed by using the Eyring equation (Mee, 1971) as in (5) below.

$$\ln K = -\frac{\Delta G^\circ}{RT} = \frac{\Delta S^\circ}{R} - \frac{\Delta H^\circ}{RT} \dots\dots\dots (5)$$

The rate constant calculations were computed according to equation (6).

$$k_{298.15K} = \frac{k_B T}{hc^\circ} e^{-\Delta^\ddagger G^\circ / RT} \dots\dots\dots (6)$$

Where $k_{(298.15K)}$ = reaction rate at temperature (298.15K), k_B = Boltzmann constant (1.380662×10^{-23} J/K), T = temperature(298.15K), h = Planck's constant (6.626176×10^{-34} Js), C° = concentration (taken to be 1), $\Delta^\ddagger G^\circ$ = Gibbs free energy of activation (kJ/mol), R = gas constant (8.31441 J/mol. K). The rate constants, k_1 , for this study was calculated to be $4.41 \times 10^{12} \text{ dm}^3 \text{ mol}^{-1} \text{ sec}^{-1}$ and $1.89 \times 10^{19} \text{ dm}^3 \text{ mol}^{-1} \text{ sec}^{-1}$ for the PM3 and DFT studies respectively.

Conclusions

The mechanism of L-Tyrosine reaction with iodine was discussed based on the Spartan '14 v1.1.0 PM3 and DFT calculation results. Comparison of the two methods used showed that the DFT calculations were more exact. The study was also able to address the ambiguity in the work previously published. In this work the most energetically stable transition state was searched and a modified reaction mechanism proposed based on that finding.

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